Communication

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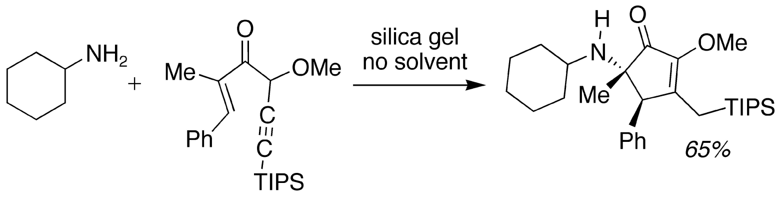
J. Am. Chem. Soc., **2005**, 127 (36), 12472-12473• DOI: 10.1021/ja053393g • Publication Date (Web): 17 August 2005



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Interrupted Nazarov Cyclization on Silica Gel

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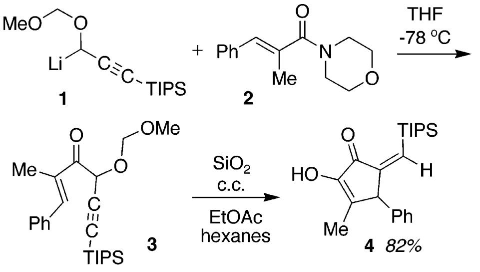
The Nazarov cyclization[1] of allenyl vinyl ketones is a facile process that takes place under very mild conditions of acid catalysis.[2] We recently reported the reaction that is summarized in eq 1.[3,4] Addition of propargyllithium species **1** to amide **2** led to enone **3** that underwent cyclization to **4** on a silica gel chromatography column (hexanes/EtOAc).[2,5] Isomerization of **3** presumably led to an allenyl vinyl ketone that cyclized spontaneously. Although a variety of enones related to **3** underwent this cyclization efficiently, we were puzzled by our observation that conversion of **3** to **4** failed to take place in the absence of solvent. It is desirable to minimize the use of organic solvents in synthesis both for reasons of economy as well as to mitigate any adverse environmental impact. Exposure of **3** to *dry* silica gel for 10 h resulted in recovery of the starting material. We reasoned that if isomerization of **3** to the allene could be induced, perhaps in the presence of added base, cyclization in the absence of solvent would quickly follow. This proved to be the case.

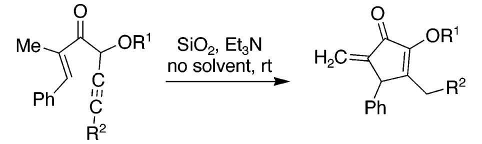


[1]

Exposure of enones **5** or **6** to activated[6] dry silica gel that had been thoroughly mixed with 1.2 equiv of triethylamine led to enones **7** (63% yield) or **8** (68% yield) after stirring for 3 h at room temperature (eq 2).[7] Presumably, the isomerization of **5** or **6** to the corresponding allenyl vinyl ketones by triethylamine had initiated a cascade of reactions through the generation of cation **9**. The process is terminated by proton loss[8] according to pathway a. Enol to ketone conversion, alkene migration, and where R^2 = TMS protiodesilylation leads to cyclopentenones that are structurally related to **4**.

Our next question was whether the presumed cationic intermediate **9** could be trapped with nucleophilic primary or secondary amines according to pathway b to generate an aminocyclopentenone. Whereas West and co-workers have reported an impressive number of interrupted Nazarov reactions in which the cationic product of the conrotation undergoes one or more C−C bond forming reactions,[9] our work describes the first example of a Nazarov reaction that is terminated by C−N bond formation.

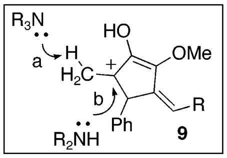
The results of Table 1 suggest that the reaction with liquid[10] aliphatic primary and secondary amines in the absence of solvent in all cases leads to good yields of product. The reaction was also examined in the presence of solvent. In the presence of silica gel and solvent (dichloromethane or THF), enone **28** reacted with **10** to give **29** in diminished yield (55 and 48%, respectively) along with larger amounts of **39** (35 and 25%, respectively). It appears that proton loss from the intermediate cation occurs more readily in the presence of solvent. Increasing the steric requirement of the α-substituent of the enone or of the amine can be predicted to favor reaction pathway a over b (see **9**). The full scope of the reaction remains to be explored; however, α-aryl enones are likely to be well tolerated. The mildness of the reaction conditions is also evidenced by the success of cyclizations with 2,2-dimethoxyethylamine **16**. No hydrolytic cleavage products of the acetal were detected under the reaction conditions.



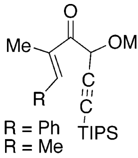
[2]

5 R^1 = Me, R^2 = TIPS
6 R^1 = MOM, R^2 = TMS

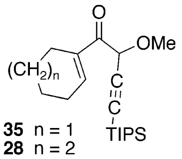
7 R^1 = Me, R^2 = TIPS *63%*
8 R^1 = MOM, R^2 = H *68%*



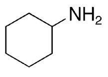
The reaction of **5** with aromatic amines (aniline and 4-diethylaminoaniline) gave rise to multiple products, including the anticipated aminocyclopentenones (ca. 20−25% yield), suggesting a competition between C−N bond formation and Friedel−Crafts alkylation.[11] Product stereochemistry in all cases is governed by approach of the amine nucleophile from the less hindered face of the cation (cf. **9**).[12]



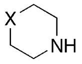
5 R = Ph
22 R = Me



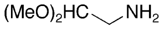
35 n = 1
28 n = 2



10



18 X = CH_2
19 X = O



16

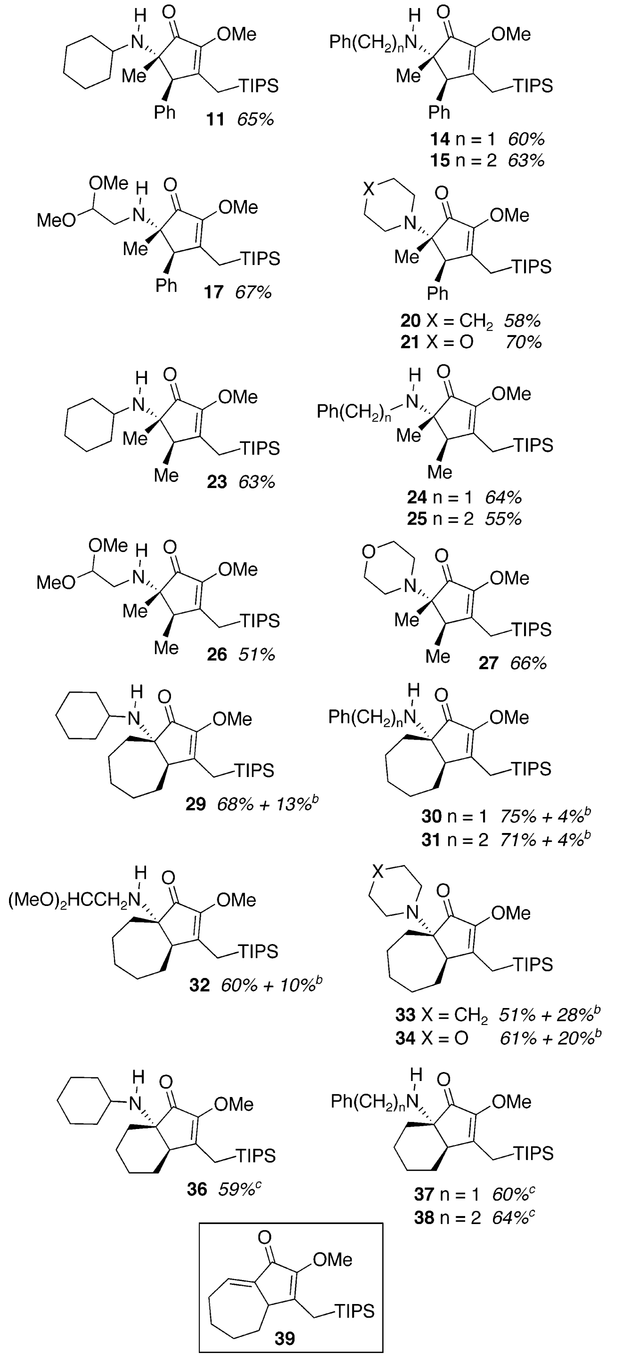
$Ph(CH_2)_nNH_2$
12 n = 1
13 n = 2

The cyclization could also be initiated by activating the propargyl vinyl ketone with Lewis acid. Of the small number of Lewis acids that were screened,[13] $Sc(OTf)_3$ was the most effective. For example, dry activated silica gel was mixed with 0.2 equiv of $Sc(OTf)_3$ and added to ketone **3** in the absence of solvent. Stirring at room temperature for 14 h led to **4** in 75% isolated yield. In this reaction, termination is through loss of the methoxymethyl cation.

It is surprising that one can trap a highly reactive intermediate, such as **9**, in a bimolecular nucleophilic process in the absence of

10.1021/ja053393g CCC: $30.25

Table 1. Aminocyclopentenones[a]



11 65%

14 n = 1 60%
15 n = 2 63%

17 67%

20 X = CH$_2$ 58%
21 X = O 70%

23 63%

24 n = 1 64%
25 n = 2 55%

26 51%

27 66%

29 68% + 13%[b]

30 n = 1 75% + 4%[b]
31 n = 2 71% + 4%[b]

32 60% + 10%[b]

33 X = CH$_2$ 51% + 28%[b]
34 X = O 61% + 20%[b]

36 59%[c]

37 n = 1 60%[c]
38 n = 2 64%[c]

39

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[a] Enones were stirred for 3 h with 16 equiv of activated SiO$_2$ and 1.2 equiv of amine. Yields of aminocyclopentenones are for two steps, addition of **1** to enamide and cyclization. [b]Yield of **39**. [c] Elimination product was formed in varying amounts in all reactions of **35** but was not isolated.

solvent. Since cation **9** has a number of decomposition pathways available, nucleophilic trapping must take place more rapidly. It, therefore, seems likely that the close proximity of amine and propargyl ketone that is required in order for isomerization to take place ensures the success of the nucleophilic addition because the reactive intermediate is generated only in the proximity of the amine. The great ease with which allenyl vinyl ketones undergo the Nazarov cyclization in the presence of even the weakest acid catalysts[14] makes it possible to use amine nucleophiles in the termination step. The cascade process results in a large increase in molecular complexity, and a number of applications in synthesis can be imagined.

Acknowledgment. Acknowledgment is made to the National Institutes of Health (GM57873) for generous support.

Supporting Information Available: Complete experimental procedures for the preparation of **7** and **11**, analytical data, and ^{1}H and ^{13}C NMR spectra for **7**−**39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) We have discussed the origin of the strong preference for formation of the *Z* exocyclic double bond isomer: Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895−9896.

(6) Silica gel was activated by heating under vacuum at 160 °C for 16 h.

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(8) The choice of methyl ethers for this work was to avoid the alternative reaction pathway, the rapid termination process that involves cleavage of methoxymethyl ethers.

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(10) A small number of experiments using solid amines did not lead to satisfactory results.

(11) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444.

(12) The methyl protons in **11** showed a positive nOe with the *ortho* phenyl protons, and the benzylic proton showed a nOe with some of the cyclohexyl protons.

(13) FeCl$_3$, CeCl$_3$, InCl$_3$, Cu(OTf)$_2$, La(OTf)$_3$, Yb(OTf)$_3$, and Sc(OTf)$_3$.

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